Ex 3, 4: Amorphous Monohydrate

Ex I: Unspecified Form

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number
WO 2004/046154 A1

(51) International Patent Classification[7]: C07D 501/05, 501/57

(21) International Application Number:
PCT/IB2003/005032

(22) International Filing Date:
10 November 2003 (10.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
848/MAS/2002 15 November 2002 (15.11.2002) IN
152/MAS/2003 26 February 2003 (26.02.2003) IN

(71) Applicant (for all designated States except US): ORCHID CHEMICALS & PHARMACEUTICALS LTD [IN/IN]; Orchid Towers, 313, Valluvar Kottam High Road, Nungambakkam, Chennai 600 034 (IN).

(72) Inventors; and

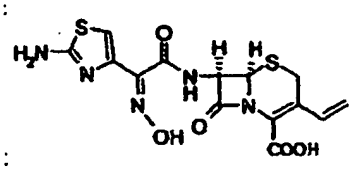
(75) Inventors/Applicants (for US only): DESHPANDE, Pandurang, Balwant [IN/IN]; C-1 "CEEBROS", Plot No. 32 (New) 1st Avenue, Indira nagar, Chennai 600 020 (IN). KHADANGALE, Bhausaheb, Pandharinath [IN/IN]; Santhi Avenue, No. 7,, Dr. Radhakrishnan Road, Thiruvanmiyur, Chennai 600 042 (IN). RAMASUBBU, Chandrasekaran [IN/IN]; No. 3 (New No.7) B1, Ramniyam Foundation, 7th Main Road, Dhandeeswarnagar, Velachery, Chennai 600 042 (IN).

(74) Common Representative: ORCHID CHEMICALS & PHARMACEUTICALS LTD; c/o Padmaja, S., Orchid Towers, 313, Valluvar Kottam High Road, Nungambakkam, Chennai 600034 (IN).

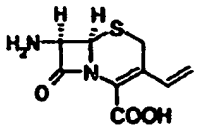
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,

[Continued on next page]

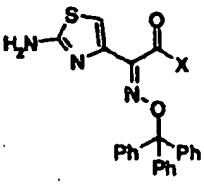
(54) Title: NOVEL AMORPHOUS HYDRATE OF A CEPHALOSPORIN ANTIBIOTIC



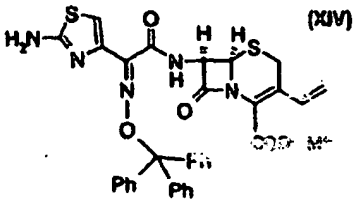
(I)



(XII)



(XIII)



(XIV)

(57) Abstract: A process for the preparation of cefdinir of the formula (I) the said process comprising the steps of :i) condensing 7-amino-3-cephem-4-carboxylic acid of the formula (XII) wherein R1 is as defined above with compound of the formula (XIII) in the presence of a tertiary amine and an organic solvent, followed by treatment with a base to produce a salt of compound formula (XIV), wherein M+ is a counter ion and ii) hydrolyzing the compound of the formula (XIV) using an acid in the presence of a solvent to produce cefdinir of formula (I).

WO 2004/046154 A1

KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

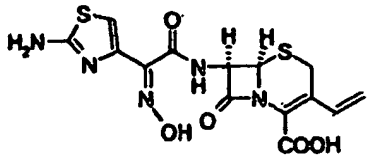
Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

NOVEL AMORPHOUS HYDRATE OF A CEPHALOSPORIN ANTIBIOTIC

Field of the Invention

The present invention relates to a novel amorphous hydrate of a cephalosporin antibiotic. More particularly, the present invention relates to novel amorphous monohydrate of cefdinir of the formula (I).



(I)

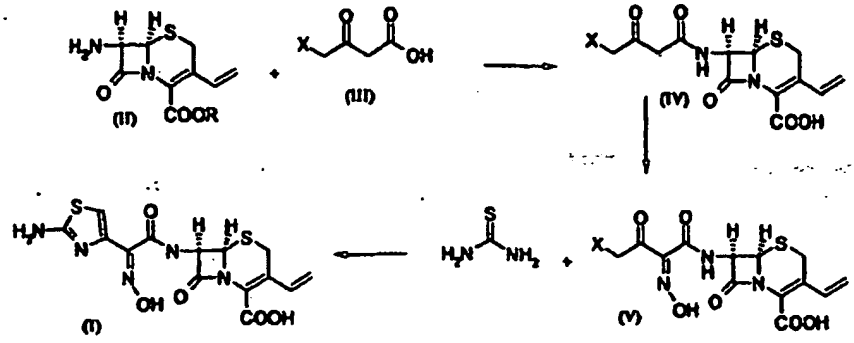
The present invention also provides a process for the preparation of the novel amorphous monohydrate of cefdinir of formula (I).

The present invention also provides new salts of compound of formula (XIV) and a process for the preparation of cefdinir using the new salts.

Background of the Invention

Cefdinir is a third generation cephalosporin antibiotic for oral administration and has a broader antibacterial spectrum over the general gram positive and gram negative bacteria, especially against *Streptococci*, than other antibiotics for oral administration.

In view of the vital antibiotic activities of cefdinir of the formula (I), various methods of preparation were reported. Cefdinir is for the first time claimed in US patent No. 4,559,334 and the nature of the product that is disclosed in this patent is described as crystalline like amorphous in subsequent US patent (US 4,935,507). This patent also discloses a process for the preparation of cefdinir as depicted in the Scheme I.



Scheme II

In the disclosed process, 7-amino-3-vinyl-3-cephem-4-carboxylic acid ester where R represents a conventional carboxy protecting group, is acylated with the reactive ester of haloacylacetic acid, which was converted to its oxime, followed by cyclization with thiourea and deprotection of the ester group to afford cefdinir. The product obtained by the process described in examples 14 and 16 is approximately 80-85 % pure. The cyclization step suffers from poor yield and affords brownish color of the thiazole derivative, which subsequently affords cefdinir, but quality and yield were inferior. Further, owing to the fact that the expensive 7-amino-3-vinyl-3-cephem-4-carboxylic acid is carried through four steps, cost of producing cefdinir is high.

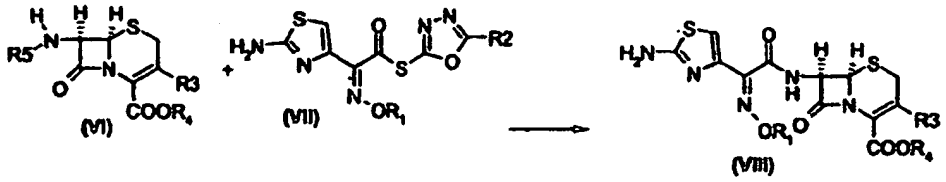
US patent number 4,935,507 claims the novel crystalline form of the cefdinir syn-isomer and a process for preparing the same. The X-ray crystallography data given in this patent is given in the following table:

2 θ ° Values	Relative Intensity
14.7	76
17.8	56
21.5	100
22.0	70
23.4	38

24.4	80
28.0	40

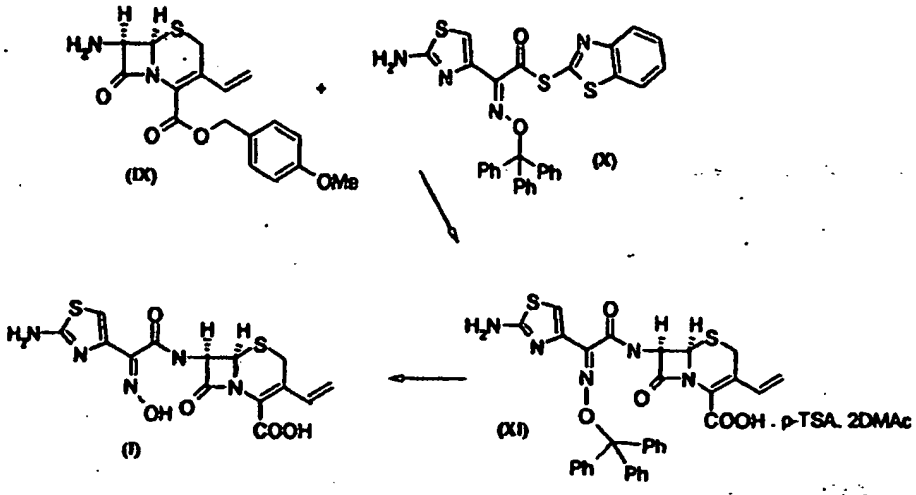
The crystalline form (Crystal A) of US 4,935,507 is prepared from the syn-isomer prepared according to the procedures described in Examples 14 and 16 of US 4,559,334.

In our US patent No. 6,388,070, we disclosed a process for preparing a compound of formula (VIII), wherein, R_1 represents H, trityl, etc., R_2 represents H, phenyl, etc., R_3 represents CH_3, $CH{=}CH_2$, etc., R_4 is H or a salt or a carboxylic protecting group; R_5 is H or trimethylsilyl; comprising acylating the compound of formula (VI) with compound of formula (VII) in the presence of an organic solvent, organic base and a silylating agent at a temperature in the range of -10 °C to +30 °C. The reaction is shown in scheme II below :



Scheme II

US patent No. 6,093,814 discloses a process for the preparation of cefdinir and its intermediate as represented in Scheme III:



Scheme III

In this process p-methoxybenzyl 7-amino-3-vinyl-3-cephem-4-carboxylate is condensed with 2-mercaptobenzothiazolyl (Z)-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetate in N,N-dimethyl acetamide, and the product obtained was treated with p-toluenesulfonic acid in the presence of a mixture of diethyl ether and methanol to get crystalline 7-[(2-amino-4-thiazolyl)-2-(Z)-(trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid.pTSA.2DMAc solvate. This process utilizes highly volatile, low-boiling and therefore industrially-not-preferred solvent, diethyl ether, for crystallizing out the above solvate. In addition, the quantity of the low-boiling solvent used is also very high ranging from 60-100 volumes, thereby adding hazard to the operations. Added to this is the fact that the recovery of these solvents from their mixture is not straight-forward.

US patent No. 6,350,869 discloses the purification of impure cefdinir through the preparation of N,N-dicyclohexylamine salt of 7-[2-amino-4-thiazolyl-2-(z)-hydroxyimino acetamido]-3-vinyl-3-cephem-4-carboxylic acid and

subsequent hydrolysis to get pure cefdinir. This process requires the preparation of crude cefdinir, conversion to N,N-dicyclohexylamine salt and then hydrolysis of the salt to get pure cefdinir, and therefore the overall yield is not attractive.

US patent No. 6,350,869 also emphasizes that cefdinir is unstable in the presence of other amines, with which, it gets heavily degraded. In addition, Yoshihiko Okamoto et al. (J. Pharm. Sci. Vol. 8(9), 976, 1996) report that cefdinir may be unstable under basic environment.

Crystalline cefdinir has limitations in formulation development as it cannot be developed into tablets.

Considering the foregoing limitations, we undertook an investigation in our lab to develop a product which is easy to handle and convenient to develop a dosage which is easily absorbable. We also parallel undertook an investigation to identify a process, which involves (i) less number of steps, (ii) the direct isolation of cefdinir, with out the need to prepare crude cefdinir in an additional step. This would permit commercializing the production of high-pure cefdinir with industrial-friendly solvent, which can further be recovered for recycling.

Objectives of the Invention

The main objective of the present invention is to provide a novel amorphous monohydrate of cefdinir which has very good bioavailability and useful in developing different dosage forms.

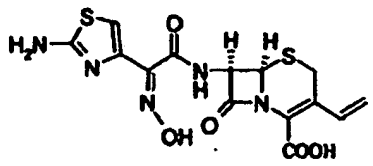
Another objective of the present invention is to provide a commercially viable process for the preparation of cefdinir and novel amorphous monohydrate of cefdinir of the formula (I), which would be easy to implement on manufacturing scale.

Yet another objective of the present invention is to provide new salts of formula (XIV), which are insoluble and stable throughout the process of

producing the cefdinir and a process for the preparation of cefdinir using these new salts.

Summary of the Invention

In an embodiment of the present invention, there is provided process for the preparation of cefdinir of the formula (I)



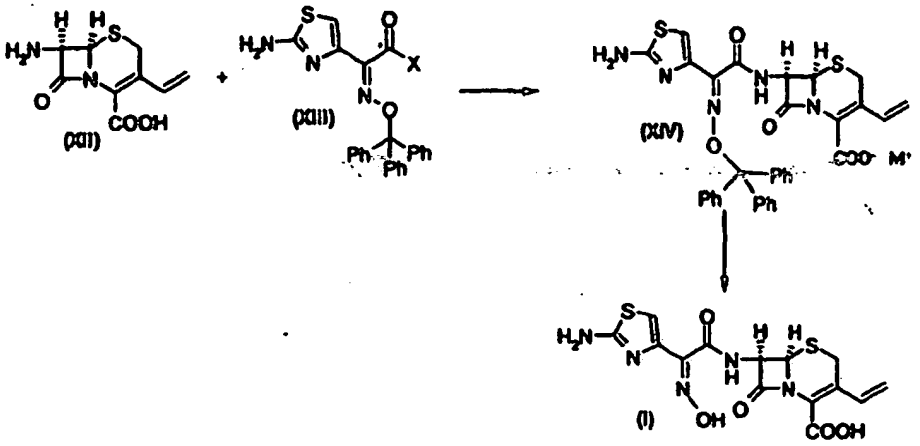
(I)

comprising the steps of :

i) condensing 7-amino-3-cephem-4-carboxylic acid of the formula (XII) wherein R_1 is as defined above with compound of the formula (XIII) in the presence of a tertiary amine and an organic solvent, followed by treatment with a base to produce a salt of compound formula (XIV), wherein M^+ is a counter ion and

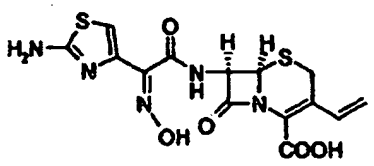
ii) hydrolyzing the compound of the formula (XIV) using an acid in the presence of a solvent to produce cefdinir of formula (I).

The reaction is shown in scheme-IV below :



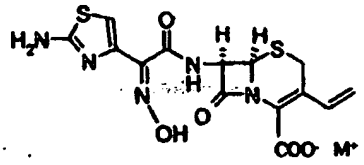
Scheme IV

Another embodiment of the present invention provides a novel amorphous monohydrate of cefdinir of the formula (I).



(I)

In yet another embodiment of the present invention, there is provided a process for the preparation of novel amorphous monohydrate of cefdinir of the formula (I) comprising hydrolyzing the compound of the formula (XV)



(XV)

comprising the steps of :

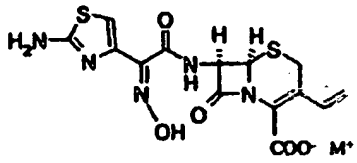
i) adding an organic solvent to compound of formula (XV),

ii) adjusting the pH of the resulting solution using an acid at a temperature in the range of 10 to 40 °C,

iii) cooing the resulting solution rapidly to –40 to 0 °and

iv) isolating the novel amorphous monohydrate of cefdinir of the formula (I).

In yet another embodiment of the present invention, there is provided a process for the preparation of novel amorphous monohydrate of cefdinir of the formula (I) comprising hydrolyzing the compound of the formula (XV)



(XV)

comprising the steps of :

i) adding an organic solvent to compound of formula (XV),

ii) cooing the resulting solution to –40 to 0 °and

iii) adjusting the pH of the resulting solution by rapid addition of an acid at a temperature in the range of 10 to 40 °C,

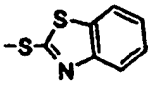
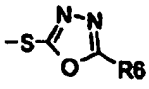
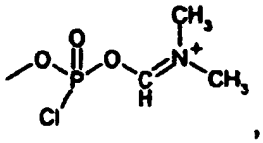
iv) isolating the novel amorphous monohydrate of cefdinir of the formula (I).

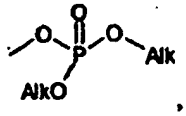
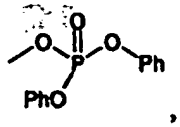
Description of Figures

Figure 1 : Comparison of powder XRD pattern of the sample prepared according to US 4,935,507 and the sample prepared according to example 3 and example 4.

Detailed description of the invention

In an embodiment of the present invention, the activation group represented by X is selected from ester, thioester, halogen atom such as chlorine,

bromine, iodine,  ,  ,  ,

 ,  , where R_6 represents (C_1-C_4)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or iso-butyl or a phenyl group; Alk group represents (C_1-C_4)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or iso-butyl.

In an other embodiment of the present invention, the counter ion represented by M is selected from sodium, potassium, lithium, magnesium, ammonium, dicyclohexylamine, N,N'-dibenzylethylenediamine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine, N,N-diisopropylamine and the like.

In another embodiment of the present invention, the tertiary amine used for condensation in step (i) is selected from triethylamine, N-methylpiperidine, N,N-diisopropylethylamine, trimethylamine and the like.

In yet another embodiment of the present invention, the organic solvent used for condensation in step (i) is selected from ethanol, methanol, isopropanol, THF, cyclohexanol, acetone, butan-2-one, acetonitrile, DMAc, water or a mixture thereof.

In yet another embodiment of the present invention, the base used for condensation in step (i) is selected from sodium hydroxide, sodium acetate, sodium 2-ethyl hexanoate, potassium hydroxide, ammonium hydroxide, ammonium acetate, calcium hydroxide, dicyclohexyl amine, N,N'-dibenzylethylenediamine diacetate, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-

diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-diazabicyclo(2.2.2)octane, N,N-diisopropylethylamine, N,N-diisopropylamine, and the like.

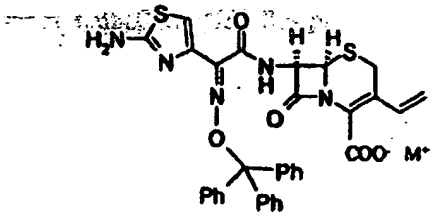
In yet another embodiment of the present invention, the organic solvent used for hydrolysis is selected from acetone, 2-butanone, methanol, isopropanol, ethanol, THF, acetonitrile, DMAc, water and the like or mixtures thereof.

In another embodiment of the present invention, the hydrolysis is carried out using acid selected from HCl, sulfuric acid, formic acid, acetic acid, aromatic/aliphatic sulfonic acids such as benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, methanesulfonic acid, triflic acid, and the like.

In yet another embodiment of the present invention, the compound of formula (I) obtained is a syn isomer.

The present invention is based on the observation that rapid cooling of the aqueous solvent solution of cefdinir to low temperatures and adding the acid rapidly produces amorphous cefdinir. The technique can be achieved either by cooling the aqueous solvent solution to low temperatures and adding the acid rapidly to adjust the pH to precipitate the amorphous product or adding the acid to adjust the pH and rapidly cooling the resultant solution to precipitate the amorphous product.

In yet another embodiment of the present invention, there is provided new salts of compounds of formula (XIV)



(XIV)

wherein M^+ represents a counter ion as defined above.

The foregoing technique has been found to be markedly attractive, both from commercial point of view, as well as from manufacturing viewpoint and affords good quality of amorphous cefdinir of the formula (I).

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure.

The present invention is illustrated with the following examples, which should not be construed as limiting to the scope of the invention.

Example 1

Step (I)

Preparation of 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino) acetate

To an ice-cold suspension of (Z)-(2-aminothioazol-4-yl)-2-(trityloxyimino)acetic acid (25 gm) in tetrahydrofuran (200 ml), triethylamine (10 gm) was added dropwise over 10 minutes at 0-5 °C. Bis-(2-oxo-oxazolidinyl)phosphinic chloride (15.4 gm) was added and stirred for one hour at 0-5 °C. To the reaction mixture 2-mercapto-5-phenyl-1,3,4-oxadiazole (9.8 gm) and triethylamine (5.0 gm) was added dropwise over 15 minutes and stirred at 0-5 °C for 6 – 7 hours. After completion of reaction, chilled water (500 ml) was added at 10-20 °C in 30 – 40 minutes and stirred at 20 °C for 2 hours. Then the slurry was cooled to 5-10 °C and stirred at this temperature for 45 minutes. The product thus obtained was filtered washed with water (100 ml) and dried at 30-35 °C for 4-5 hours to yield the title compound (50 gm, water content is 40%).

Step (ii)

Preparation of potassium 7β-[2-(2-amino-4-thiazolyl)-2-(Z-trityloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylate

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (25 gm) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetate (155 gm, water content is 40 %) in N,N-dimethylacetamide (150 ml), triethylamine (23 gm) was added drop-wise at 10±2 °C over 30-45 minutes and the resulting mixture was stirred at 20±2 °C for 6-8 hours. The reaction was monitored by HPLC. After completion of the reaction, tetrahydrofuran (125 ml), 10% sodium chloride solution (250 ml) and ethyl acetate (250 ml) were added at 25 °C and stirred for 20 min. The aqueous layer was separated and washed with ethyl acetate (250 ml). To the aqueous layer, ethyl acetate (500 ml) was added, cooled to 10 - 15 °C, and the pH was adjusted to 2.8-3.0 by 1:1 HCl in 30 min. The layers were separated and to the ethylacetate layer, 12 % (w/v) methanolic potassium hydroxide solution (60 ml) was added dropwise in 30 min at 25 °C, and stirred for 45 min. The resulting slurry was filtered, washed with ethyl acetate (150 ml) followed by acetone (150 ml) and dried at 30-35 °C under vacuum to obtain the title compound (45 gm, HPLC Purity >99.0%).

Step (iii)

Preparation of 7β-[2-(2-amino-4-thiazolyl)-2-(Z-hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid

A mixture of potassium 7β-[2-(2-amino-4-thiazolyl)-2-(Z-trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (25 gm) and activated carbon (2.5 gm) was added to an aqueous acetone solution (1:1, 70 ml) containing p-toluenesulphonic acid (17.7 gm) at 50 °C. The reaction mixture was heated to

70 °C in 20 minutes and maintained at this temperature for 35 minutes. After completion of the reaction, chilled ethylacetate (200 ml) having temperature –15 °C was added to the reaction mixture to reduce the temperature to 30-35 °C. The carbon was filtered and the carbon bed was washed with water (50 ml). The filtrate was diluted with water (200 ml), warmed to 35 °C and pH of the solution was adjusted to 6.0 –6.5 using aqueous ammonia solution (20%). The aqueous layer was separated and treated with carbon (2.0gm) at 35°C for 35 min. The carbon was filtered and the carbon bed was washed with water (50 ml). Acetone (25 ml) was added to the filtrate and 10 % (w/v) solution of sulphuric acid was added dropwise to bring down the pH from 4.5 to 2.8 at 33-35 °C, stirred for 30 minutes and adjusted the pH again to 2.6. The resulting slurry was stirred for 15 – 20 minutes at 33-35 °C, cooled to 20-25°C, and stirred for 30 minutes. The product thus obtained was filtered, washed with water (50 ml) and dried at 35 °C under vacuum for 3-4 hours to get the title compound (9.0 gm, HPLC purity < 99%).

Example 2

Step (i)

Preparation of 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino) acetate

To an ice-cold suspension of (Z)-(2-aminothioazol-4-yl)-2-(trityloxyimino)acetic acid (25 gm) in tetrahydrofuran (200 ml), triethylamine (10 gm) was added dropwise over 10 minutes at 0-5 °C. Bis-(2-oxo-oxazolidinyl)phosphinic chloride (15.4 gm) was added and stirred for one hour at 0-5 °C. To the reaction mixture 2-mercapto-5-phenyl-1,3,4-oxadiazole (9.8 gm) and triethylamine (5.0 gm) was added dropwise over 15 minutes and stirred at 0-5 °C for 6 – 7 hours. After

completion of reaction, chilled water (500 ml) was added at 10-20 °C in 30 – 40 minutes and stirred at 20 °C for 2 hours. Then the slurry was cooled to 5-10 °C and stirred at this temperature for 45 minutes. The product thus obtained was filtered washed with water (100 ml) and dried at 30-35 °C for 4-5 hours to yield the title compound (50 gm, water content is 40%).

Step (ii)

Preparation of potassium 7β-[2-(2-amino-4-thiazolyl)-2-(Z-trityloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylate

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (5 gm) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetate (24.2 gm) in tetrahydrofuran (40 ml) and water (5 ml), triethylamine (4.6 gm) was added drop-wise at 20±2 °C over 10-15 minutes and the resulting mixture was stirred at 30±2 °C for 6-8 hours. The progress of the reaction was monitored by HPLC. After completion of reaction, ethylacetate (100 ml) and water (75 ml) were added at 30±2 °C and stirred for 20 min. The aqueous layer was separated and washed with ethyl acetate (75 ml). To the aqueous layer, ethylacetate (150 ml) was added, cooled to 10 - 15 °C, and the pH was adjusted to 2.8-3.0 by 1:1 HCl solution in 25-30 min. To the separated ethylacetate layer, acetone (50 ml) and a methanolic potassium hydroxide solution (7.5 % w/v, 20 ml) were added dropwise in 25-30 min at 25 –27 °C and stirred for further 45 min. The resulting slurry was filtered, washed with acetone (2 X 25 ml) and dried at 30-35 °C under vacuum to obtain the title compound (5.0 gm, HPLC Purity >99.0 %).

Step (iii)

Preparation of 7β-[2-(2-amino-4-thiazolyl)-2-(Z-hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid

A mixture of potassium 7β-[2-(2-amino-4-thiazolyl)-2-(Z-trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (25 gm) and activated carbon (2.5 gm) was added to an aqueous acetone solution (1:1, 70 ml) containing p-toluenesulphonic acid (17.7 gm) at 50 °C. The reaction mixture was heated to 70 °C in 20 minutes and maintained at this temperature for 35 minutes. After completion of the reaction, chilled ethylacetate (200 ml) having temperature –15 °C was added to the reaction mixture to reduce the temperature to 30-35 °C. The carbon was filtered and the carbon bed was washed with water (50 ml). The filtrate was diluted with water (200 ml), warmed to 35 °C and pH of the solution was adjusted to 6.0 –6.5 using aqueous ammonia solution (20%). The aqueous layer was separated and treated with carbon (2.0gm) at 35°C for 35 min. The carbon was filtered and the carbon bed was washed with water (50 ml). Acetone (25 ml) was added to the filtrate and 10 % (w/v) solution of sulphuric acid was added dropwise to bring down the pH from 4.5 to 2.8 at 33-35 °C, stirred for 30 minutes and adjusted the pH again to 2.6. The resulting slurry was stirred for 15 – 20 minutes at 33-35 °C, cooled to 20-25°C, and stirred for 30 minutes. The crystals thus obtained was filtered, washed with water (50 ml) and dried at 35 °C under vacuum for 3-4 hours to get the title compound (9.0 gm, HPLC purity < 99%).

Example 3

Preparation of (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in amorphous hydrate form

Ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (20 gm) was added to a mixture of water (250 ml) and acetone (80 ml) and warmed to 33-35 °C. This aqueous solution was treated with activated charcoal and EDTA at 35 °C for 40 minutes. The carbon was filtered and the carbon bed was washed with water (70 ml). This aqueous acetone solution was cooled to -30 °C and a (10 %) solution of aqueous sulphuric acid was added rapidly, stirred for 30 minutes and warmed to 0-2 °C. The product thus obtained was filtered at 0-2 °C, washed with cold-water (100 ml) and dried at 40-45 °C under vacuum for 5-6 hours to get (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (6.0 gm, HPLC quality 89.0 %, water content 4-5 %).

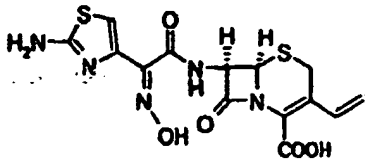
Example 4

Preparation of (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in amorphous hydrate form

Ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (20 gm) was added to a mixture of water (250 ml) and acetone (80 ml) and warmed to 33-35 °C. This aqueous solution was treated with activated charcoal and EDTA at 35 °C for 40 minutes. The carbon was filtered and the carbon bed was washed with water (70 ml). The pH of this aqueous acetone solution was adjusted to 0.6 at 33-35 °C using a (10 %) solution of aqueous sulphuric acid. This solution was cooled rapidly to -10 °C and stirred for 30 minutes. The product thus obtained was filtered at -10 °C, washed with cold-water (100 ml) and dried at 40-45 °C under vacuum for 5-6 hours to get (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (6.0 gm, HPLC quality 93.0 %, water content 4-5 %).

Claims :

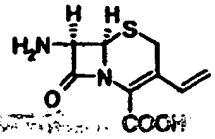
1. A process for the preparation of cefdinir of the formula (I)



(I)

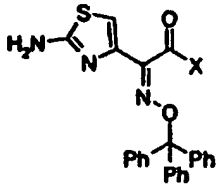
the said process comprising the steps of :

i) condensing 7-amino-3-cephem-4-carboxylic acid of the formula (XII)



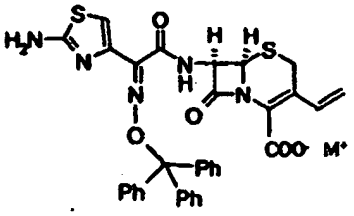
(XII)

wherein R_1 is as defined above with compound of the formula (XIII)



(XIII)

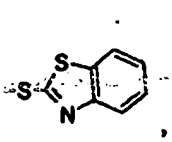
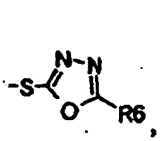
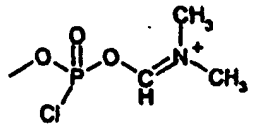
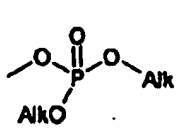
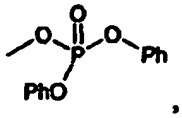
in the presence of a tertiary amine and an organic solvent, followed by treatment with a base to produce a salt of compound formula (XIV),



(XIV)

wherein M^+ is a counter ion and

ii) hydrolyzing the compound of the formula (XIV) using an acid in the presence of a solvent to produce cefdinir of formula (I).

2. The process as claimed in claim 1, wherein activation group represented by X is selected from ester, thioester, halogen atom such as chlorine, bromine, iodine,  ,  ,  ,  ,  , where R_6 represents (C_1-C_4)alkyl group or phenyl group; Alk group represents (C_1-C_4)alkyl.

3. The process as claimed in claim 1, wherein the counter ion represented by M is selected from sodium, potassium, lithium, magnesium, ammonium, dicyclohexylamine, N,N'-dibenzylethylenediamine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine or N,N-diisopropylamine.

4. The process as claimed in claim 1, wherein the tertiary amine is selected from triethylamine, N-methylpiperidine, N,N-diisopropylethylamine, trimethylamine and the like.

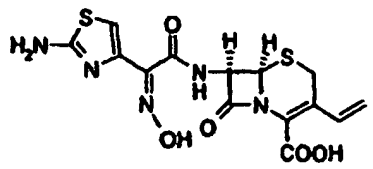
5. The process as claimed in claim 1, wherein the organic solvent used in step (i) is selected from ethanol, methanol, isopropanol, THF, cyclohexanol, acetone, butan-2-one, acetonitrile, DMAc, water or a mixture thereof.

6. The process as claimed in claim 1, wherein the organic solvent used in step (ii) is selected from acetone, 2-butanone, methanol, isopropanol, ethanol, THF, acetonitrile, DMAc, water and the like or mixtures thereof.

7. The process as claimed in claim 1, wherein the acid is selected from HCl, sulfuric acid, formic acid, acetic acid or aromatic/aliphatic sulfonic acids.

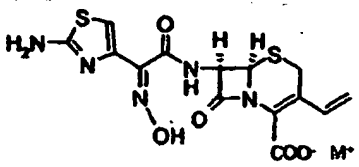
8. The process as claimed in claim 1, wherein the compound of formula (I) obtained is a syn isomer.

9. A novel amorphous monohydrate of cefdinir of the formula (I)



(I)

10. The process for the preparation of novel amorphous monohydrate of cefdinir of the formula (I) as claimed in claim 9, comprising hydrolyzing the compound of the formula (XV)



(XV)

comprising the steps of :

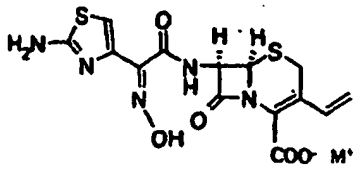
i) adding an organic solvent to compound of formula (XV),

ii) adjusting the pH of the resulting solution using an acid at a temperature in the range of 10 to 40 °C,

iii) cooing the resulting solution rapidly to –40 to 0 °and

iv) isolating the novel amorphous monohydrate of cefdinir of the formula (I).

11. The process for the preparation of novel amorphous monohydrate of cefdinir of the formula (I) as claimed in claim 9, comprising hydrolyzing the compound of the formula (XV)



(XV)

comprising the steps of :

i) adding an organic solvent to compound of formula (XV),

ii) cooing the resulting solution to –40 to 0 °and

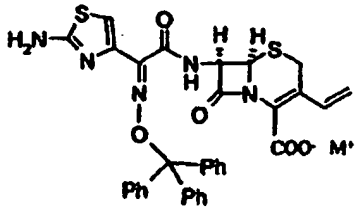
iii) adjusting the pH of the resulting solution by rapid addition of an acid at a temperature in the range of 10 to 40 °C,

iv) isolating the novel amorphous monohydrate of cefdinir of the formula (I).

12. The process as claimed in claims 10 and 11, wherein the organic solvent is selected from acetone, 2-butanone, methanol, isopropanol, ethanol, THF, acetonitrile, DMAc, water and the like or mixtures thereof.

13. The process as claimed in claims 10 and 11, wherein the acid is selected from HCl, sulfuric acid, formic acid, acetic acid or aromatic/aliphatic sulfonic acids.

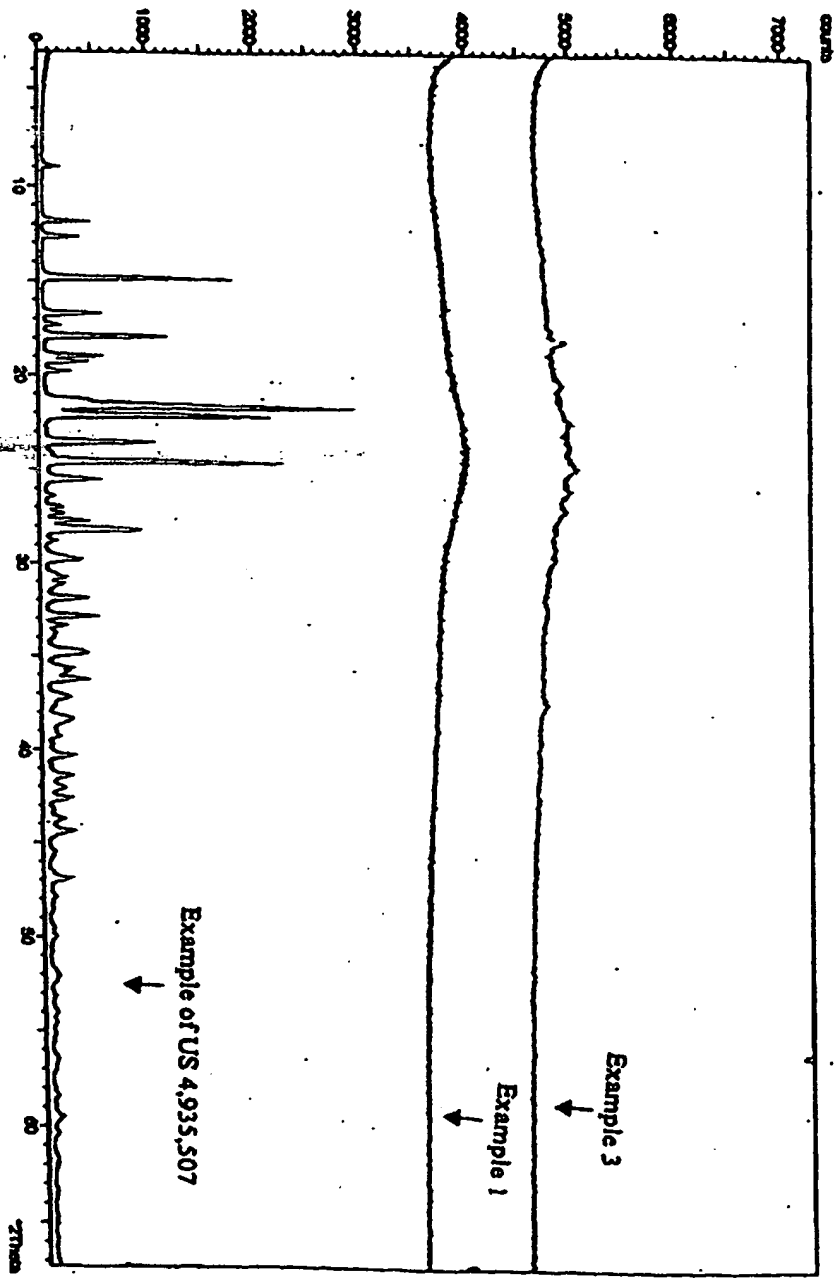
14. A compound of compound formula (XIV),



(XIV)

wherein M^+ represents a counter ion.

FIG. 1/1


1000
2000
3000
4000
5000
6000
7000
counts
0
10
20
30
40
50
60
°2Theta
Example of US 4,935,507
Example 1
Example 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB 03/05032

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/06 C07D501/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 79211 A (OTSUKA KAGAKU KK) 25 October 2001 (2001-10-25) claims; example 1	1,9,14
Y	WO 99 51607 A (DECRISTOFORO MARTIN ;BIOCHEMIE GMBH (AT); STURM HUBERT (AT); LUDES) 14 October 1999 (1999-10-14) page 1; claims; examples	1-8
Y	US 6 388 070 B1 (DESHPANDE PANDURANG BALWANT ET AL) 14 May 2002 (2002-05-14) cited in the application claims; examples	1-8
P,Y	WO 02 098884 A (CHANG YOUNG KIL ;KIM CHEOL KYUNG (KR); KIM HONG SUN (KR); LEE GWAN) 12 December 2002 (2002-12-12) claims; examples	1-8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 2004	01/03/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB 03/05032

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03 050124 A (KUMAR NEELA PRAVEEN ;KUMAR YATENDRA (IN); PRASAD ASHOK (IN); PRASA) 19 June 2003 (2003-06-19) claims; examples	1-8,14

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatio[illegible] pplication No
PCT/IB 03/05032

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0179211	A	25-10-2001	JP	2001294590 A	23-10-2001
			CN	1134445 B	14-01-2004
			EP	1273587 A1	08-01-2003
			WO	0179211 A1	25-10-2001
WO 9951607	A	14-10-1999	AT	406773 B	25-08-2000
			AT	57598 A	15-01-2000
			AU	3603599 A	25-10-1999
			BR	9909898 A	26-12-2000
			CA	2326441 A1	14-10-1999
			CN	1134446 B	14-01-2004
			WO	9951607 A2	14-10-1999
			EP	1068211 A2	17-01-2001
			ID	26210 A	07-12-2000
			JP	2002510694 T	09-04-2002
			TR	200002838 T2	21-02-2001
			US	2003208065 A1	06-11-2003
			ZA	200004899 A	14-10-2001
US 6388070	B1	14-05-2002	CA	2433783 A1	11-07-2002
			EP	1347970 A1	01-10-2003
			WO	02053563 A1	11-07-2002
WO 02098884	A	12-12-2002	KR	2002092612 A	12-12-2002
			WO	02098884 A1	12-12-2002
WO 03050124	A	19-06-2003	WO	03050124 A1	19-06-2003